REMARKS

Claims 1 to 21 are pending.

Present amendment revises Claims 1 to 21 and adds new Claims 22 to 44.

Applicants reserve the right to file continuation applications with claims directed to the subject matter of originally-filed Claims 1-21.

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I. BACKGROUND ON EPLERENONE

Eplerenone is the active ingredient in INSPRA™, a pharmaceutical product that was commercially launched in January 2004. One of the clinical studies submitted in support of FDA registration of INSPRA™ was a morbidity and mortality study referred to as the EPHESUS study. In the EPHESUS study, Eplerenone was administered on top of standard of care therapy to patients with severe heart failure.

The results of the EPHESUS study are reported in the New England Journal of Medicine, volume 348(14), 1309-21 (4 April 2003). A copy of this article is attached to this response. The article reports that "[t]he addition of eplerenone to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure." Id. At 1309. These results confirm Applicants' assertions (see, e.g., Biological Evaluation I and Biological Evaluation II contained in the application at pages 112 to 127 and pages 128 to 164, respectively) regarding the benefit of the claimed combination therapy to patients with a cardiovascular disorder.

II. Revised Claims 1-21 and New Claims 22-44

Applicants have: cancelled originally pending Claims 3-5, 11,14,15,19 and 20; amended originally pending Claims 1,2,6,9,10, 12,13,16; retained originally pending Claims 7,8,17 and 18; and added new Claims 22 to 44. The revised and added claims are similar to, but further clarify, originally pending Claims 1-21.

Amended, sole independent Claims 1 and 9 now specify that:

(a) the epoxy-steroidal aldosterone receptor antagonist of the combination is eplerenone, and

(b) the therapeutic combination also includes a loop diuretic, in addition to eplerenone and an ACE inhibitor.

Support for new Claims 22-44 is found, for example, in originally pending Claims 1-21 and in the specification, as follows:

New Claims 22-44	Originally Pending Claims 1-21	Specification Page(s)/Line(s))
22	21	P.40,L.9-13
23	--	P.17,L.21-30;P.22,L.28-30
24	1	P.20,L.26-P.21,L.28
25	1	P.20,L.26-P.21,L.28
26	1	P.20,L.26-P.21,L.28
27	1	P.20,L.26-P.21,L.28
28	1	P.20,L.26-P.21,L.28
29	1	P.20,L.26-P.21,L.28
30	1	P.20,L.26-P.21,L.28
31	1	P.20,L.26-P.21,L.28
32	1	P.20,L.26-P.21,L.28
33	1	P.20,L.26-P.21,L.28
34	--	P.17,L.21-30;P.22,L.28-30
35	9	P.20,L.26-P.21,L.28
36	9	P.20,L.26-P.21,L.28
37	9	P.20,L.26-P.21,L.28
38	9	P.20,L.26-P.21,L.28
39	9	P.20,L.26-P.21,L.28
40	9	P.20,L.26-P.21,L.28
41	9	P.20,L.26-P.21,L.28
42	9	P.20,L.26-P.21,L.28
43	9	P.20,L.26-P.21,L.28
44	9	P.20,L.26-P.21,L.28

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III. Related Patents and Co-Pending Applications

Applicants wish to point out to the Office the following commonly owned patent and co-pending applications that relate to

combination therapy (and corresponding combinations) employing eplerenone, an ACE inhibitor and, optionally, a diuretic:

(1) U.S. 6,410,524;

(2) U.S. Application 10/077,134 (allowed but not issued);

(3) U.S. Application 10/440,691;

(4) U.S. Application 10/637,070; and

(5) Continuation filed 8 JAN 04 from U.S. Application 10/077,134 (see above)

* * *

IV. Rejection Under 35 USC §112(1)

The Office has objected to the specification and rejected Claims 1-4, 6-14 and 16-21 under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to make and/or use the invention and thereby failing to provide an enabling disclosure. Specifically, the Office asserts that '[a]pplicant fails to set forth the criteria that defines those compounds providing 'epoxy-steroidal aldosterone receptor antagonist' activity useful for practicing the invention herein envisioned.", and that "only a limited number of those compounds providing 'epoxy-steroidal aldosterone receptor antagonist' activity examples are set forth, thereby failing to provide sufficient working examples."

Applicants have amended the claims to specify that the epoxy-steroidal aldosterone receptor antagonist is eplerenone. The application states that Eplerenone is a preferred epoxy-steroidal aldosterone receptor antagonist. See Application, page 24, lines 1 to 6; and Table 1, Compound # 1.

Accordingly, the objection to the specification and rejection of now pending Claims 1,2,6-10,12,13,16-18, and 21 under 35 USC §112, first paragraph, as discussed above should be withdrawn.

* * *

V. Rejection Under 35 USC §112(2)

The Office has rejected Claims 1-4, 6-14 and 16-21 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim Applicants' invention. Specifically, the Office asserts that the rejected claims "are rendered indefinite by the phrase 'epoxy-steroidal aldosterone receptor antagonist' and thereby failing to clearly set forth the metes and bounds of the patent protection desired.", and that "[a]pplicants term fails to clearly define the subject matter encompassed by the instant claims, thus is properly rejected under 35 USC 112, second paragraph."

As noted above, applicants have amended the claims to specify that the epoxy-steroidal aldosterone receptor antagonist is eplerenone. The application states that eplerenone is a preferred epoxy-steroidal aldosterone receptor antagonist. See Application, page 24, lines 1 to 6; and Table 1, Compound # 1.

Accordingly, the rejection of now pending Claims 1,2,6-10,12,13,16-18, and 21 under 35 USC §112, second paragraph, should be withdrawn.

* * *

VI. Rejection Under 35 USC §103(a) over Delyani, Sharpe et al., and Schoelkens et al.

The Office has rejected Claims 1-21 under 35 USC §103(a) as being unpatentable over Delyani ("Delyani"), Sharpe et al. ("Sharpe")and Schoelkens et al ("Schoelkens"). Applicants respectfully disagree and request withdrawal of this rejection.

It is well accepted (e.g., MPEP §2142) that in order to establish a prima facie case of obviousness the Office must show:

(1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings,

(2) there is a reasonable expectation of success if the modification or combination is carried out, and

(3) the reference, or references when combined, teach or suggest all the claim limitations.

Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. There is no reference or even a suggestion of using eplerenone or a loop diuretic, or any other combination therapy, in either Sharpe or Schoelkens. Delyani, either alone or in combination with Sharpe and/or Schoelkens, also does not teach or suggest the claimed invention, and does not provide a reasonable expectation of success.

Claims 1 and 9 (the independent claims rejected under §103) of the present application have been amended to clarify that the method involves a therapeutic combination of eplerenone, an ACE inhibitor and a loop diuretic. However, Delyani teaches that a loop diuretic can be harmful, stating that "[p]atients who lack or have only minor CHF symptoms but exhibit left ventricular

dysfunction may have an adverse effect when treated with loop diuretics." (Column 1, page 756). If anything, Delyani teaches away from treating heart failure patients with a loop diuretic, as specified in the amended claims.

Further, it should be noted that the drug combinations claimed in this invention have been and currently are considered to be potentially toxic, particularly regarding the interaction between an ACE inhibitor and an aldosterone antagonist. As cited in examples of references shown below, this combination is not recommended for patients and therefore standard of care teaches *against* the drug combination in the present invention that, contrary to these teachings, discloses a positive benefit to patients administered the combinations claimed in this application.

References Teaching Against Therapeutic Combinations of an Aldosterone Antagonist with an ACE Inhibitor:

Goodman & Gilman's "The Pharmacological Basis of Therapeutics", Ninth Edition, 1996.

1. "Spironolactone may cause life-threatening hyperkalemia… is contraindicated in patients at risk of developing hyperkalemia… because of administration of other medications." p.708.

2. " ACE inhibitors also increase the serum potassium concentration.….
   Potassium sparing diuretics" (spironolactone) "should be administered cautiously to patients receiving vasodilators of this class." (ACE inhibitors). p.822.

Clinician's Manual on Chronic Heart Failure, S. W. Davies and J. Bayliss, 1994.

3. Side effect of ACE inhibitor therapy in chronic heart failure - "Hyperkalemia NB: ACE inhibitors should not be administered with potassium-sparing diuretics". p.39.

4. Safety of ACE inhibitor in general practice: "Hyperkalemia…Potassium-sparing diuretics, such as amiloride, triamterene and spironolactone should be stopped when ACE inhibitors are commenced." p. 58.

Physicians' Desk Reference, 53rd Edition, 1999.

5. "Vasotec (enalapril) attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride)…may lead to significant increases in serum potassium….Potassium sparing agents should generally not be used in patients with heart failure receiving Vasotec." Vasotec, p. 1918.

6. "Hyperkalemia….can cause cardiac irregularities, which may be fatal….Concomitant administration of potassium-sparing diuretics with ACE inhibitors or indomethacin has been associated with severe hyperkalemia." Aldactone, p. 2929.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the present claims over Delyani, Sharpe and/or Schoelkens. Accordingly, the aforementioned §103 objection should not be maintained against pending Claims 1,2,6-10,12,13,16-18, and 21.

* * *

Pending Claims 1,2,6-10,12,13,16-18,21 and 22-44, should now be in condition for allowance.

Favorable consideration and early allowance of Claims 1,2,6-10,12,13,16-18,21 and 22-44 is requested. Applicants respectfully request a three-month extension of time to and including March 23, 2004 for filing a response to the September 23, 2003 Office Action in this matter. The Commissioner is hereby authorized to charge the $950.00 fee for the requested three-month extension of time under 37 C.F.R. 1.16 and 1.17, together with any fees that may be required during the entire pendency of this application, to Deposit Account No. 19-1025.

Respectfully submitted,

Joseph R. Schuh

Joseph R. Schuh
Agent for Applicants
Registration No. 48,180

PHARMACIA CORPORATION
Global Patent Department
P.O. Box 1027
St. Louis, MO 63006
314-274-8182
FAX: 314-274-9095

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